Synopsis

Name of Research Scholar: Ritu **Name of Supervisor:** Prof. Ravichandiran V

Registration No.: 09/Ph.D./DPSRU/2019

Title of Thesis: "Protective effect of bioflavonoids in diabetic complications via modulating NF-κB/MMP-9/TIMPs pathway using STZ induced diabetic Rat Model"

Abstract of work done

Introduction: The proposed work focused on evaluating the protective effect of a bioflavonoid combination (genistein enriched soyabean extract (300 mg/kg), gingerol rich ginger extract (75 mg/kg), and hesperetin (100 mg/kg) in the management of diabetic complications via modulation of these two NF-κB, MMP-9/TIMPs, and IRS-1/GLUT-4 signaling pathway.

Objective:

1. To study the protective effect of bioflavonoid combination on the retina in streptozotocin-induced diabetic retinopathy in neonatal diabetic rats.

2.To study the protective effects of bioflavonoid combination on the heart in streptozotocin-induced diabetic cardiomyopathy in neonatal diabetic rats.

3.To evaluate the effect of bioflavonoid combination on nephron in streptozotocin-induced diabetic nephropathy in neonatal diabetic rats.

4. Development of suitable dosage form for intended clinical use

Milestones of the thesis with DSRC AND URAC dates

DSRC	Date	URAC	Date
DSRC 1ST	19-Feb-2021	1st	2022
DSRC 2ND	16/Nov/2022	2nd	11/4/23
DSRC 3rd	7th Nov 2023	3rd	10/6/24

DSRC 4th	14th Oct 2024	4th	24/3/25

Methodology: Type II diabetes was induced in 5-day-old neonatal pups by using streptozotocin (STZ) 90 mg/kg; i.p. After 6 weeks of induction of diabetes blood glucose was measured and rats with blood glucose more than 160 mg/dl were considered in the study. There were three groups' normal control, diabetic, and treatment in the study. The treatment group received a bioflavonoid combination (genistein enriched soyabean extract (300 mg/kg), gingerol rich ginger extract (75 mg/kg), and hesperetin (100 mg/kg); p.o for 24 weeks. HOMA-IR, serum insulin, and OGTT were measured after 24 weeks of induction of diabetes in all three groups. In diabetic retinopathy, functional (fundus photography, fluorescein angiography, flat mount of retina, and trypsin digestion of retina), molecular (gel zymography, IHC, western blot, and PCR), and biochemical (TAC) parameters were evaluated. However, in diabetic cardiomyopathy functional parameters like ECG, ECHO, and hemodynamic parameters were evaluated. Moreover, myocardial enzymes (CK-MB, LDH, hsCRP) and serum cholesterol and triglyceride were also evaluated. Various molecular parameters like IHC, gel zymography, western blot, and PCR were done for protein and mRNA expression. Subsequently in diabetic nephropathy serum and urine analyses were done for diagnosis of early-stage diabetic nephropathy and renal damage. Besides, molecular parameters like western blot, IHC, gel zymography and PCR were also done for protein and mRNA expression analysis. In vitro studies were also conducted to assess the insulin-secreting activity of these flavonoids in pancreatic cell line RIN 5F.

Results:

Initially, *in silico* studies with Schrodinger software reveal that genistein, gingerol, and hesperitin demonstrated strong binding affinities for MMP-9, TIMPs, and NF-κB, surpassing estradiol and indicating potential as modulators of biomarkers relevant to diabetic complications. To validate these findings, in vivo studies using a Type II diabetic rat model treated with a bioflavonoid combination for 24 weeks showed promising protective effects in diabetic retinopathy, cardiomyopathy, and nephropathy. HOAM-IR, AUC in the oral glucose

tolerance test (OGTT) and blood glucose were significantly decreased in the treatment group as compared to the diabetic group Bioflavonoids attenuated retinal changes in diabetic retinopathy, reduced neurovascular complications, and enhanced insulin sensitivity by modulating pathways like NF-κB/MMP-9 and IRS-1/GLUT-4. Besides in cardiomyopathy, bioflavonoid combination reduced inflammatory markers, serum cholesterol, triglyceride and improved cardiac function metrics. There was also a significant improvement in hemodynamic and ECG parameters after 24 weeks treatment with bioflavonoids. Moreover, there was a downregulation of NF-κB, MMP-9, and TGF-β biomarkers in the treatment group as compared to the diabetic group as revealed by western blot, PCR, IHC while in nephropathy, they modulated oxidative stress and ECM remodeling, improving renal health markers and restoring balance in MMP-9 and TIMP-1 expression. There was also a significant improvement in GLUT-4 and TIMP-1 expression whereas that of NF- κB, TGF-β were reduced as revealed by western blot and PCR. Additionally, these flavonoids were found to increase insulin secretion in pancreatic RIN5F cell line and reduces the expression of MMP-9 and NF- κB IN 3T3L1 cell line suggesting its role as insulin enhancer and reduces adipogenesis. These findings suggest that bioflavonoids hold potential for comprehensive therapeutic interventions in managing diabetic complications through anti-inflammatory, anti-angiogenic, and antioxidant mechanisms, meriting further research and clinical trials.

Conclusions: Treatment with a bioflavonoid combination for 24 weeks mitigates the diabetic complications via modulation of NF-κB, MMP-9, TIMPs pathway and also potentiation of IRS-1, GLUT-4 signaling.

Scientific relevance and impact of the results on scientific potential of the country. With a burden of 17% of the total cases of diabetes, India has now been regarded as the "Diabetes Capital of the World." Sight threatening and life-threatening complications of diabetes are now claiming numerous human lives. Indian food culture that involves consumption of various seasonal herbs and fruits has been known to have various health benefits. The results of the present project work substantiate the vegetable and fruit intake rich in flavonoids. The flavonoid combination used here proved to mitigate diabetic retinopathy, cardiomyopathy, and nephropathy. The intermediate results of the current study are encouraging, and additional ongoing research would reveal multiple biochemical mechanisms through which

flavonoids could function. Moreover, the development of a suitable formulation using the combination could lead to the prevention of diabetic complications.

Impact of the Work and possible Future Work

The ultimate goal is to translate the findings into a viable therapeutic intervention for diabetic complications. By refining the formulation and expanding the scope of biomarker targets, the work aims to provide strong evidence for the bioflavonoid combination's efficacy, paving the way for clinical trials and, potentially, a novel treatment for managing diabetic complications. We expect that a suitable formulation can be developed and with the help of Pharmaceutical company pre clinical regulatory toxicity studies followed by clinical trials can be carried out.

Recommendations of URAC after 4th DSRC	**Compliance**
4th DSRC report of Ms. Ritu approved for thesis submission	The presentation of the report is in compliance with the designed format.

Overall progress of the work

S.no	Objectives	Task	Current status of objectives	20221	2022-2023	2023-2024
1	Induction of diabetes	Selection of suitable type 2 animal diabetic Model	Completed	✓	✓	
2.	To study the protective effect of bioflavonoid combination on the retina in streptozotocin-induced diabetic retinopathy in neonatal diabetic rats.	Fundus Photography	Completed		✓	
		FITC dextran			✓	
		TAC			✓	
		IHC of NF-kB			✓	
		Gel zymography			✓	
		TUNEL assay				✓
		RT-PCR of MMP-9,TIMPs and IRS-1				✓
		Histopathology				✓
3.	To study the protective effects of bioflavonoid combination on the heart in streptozotocin-induced diabetic cardiomyopathy in neonatal diabetic rats.	Haemodyamic	Completed		✓	
		ECG			✓	
		TAC			✓	
		Gel zymography			✓	
		RT-PCR of MMP-9,TIMPs and IRS-1				✓
		Histopathology				✓
7.	To evaluate the effect of bioflavonoid combination on nephron in streptozotocin-induced diabetic nephropathy in neonatal diabetic rats.	Urine analysis	Completed		✓	
		TAC			✓	
		Gel zymography			✓	
		RT-PCR of MMP-9,TIMPs and IRS-1	Completed			✓
		Histopathology				✓
5.	Development of suitable dosage form for intended clinical use.		Completed			✓

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Submission Information

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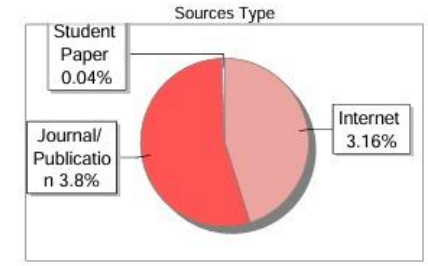

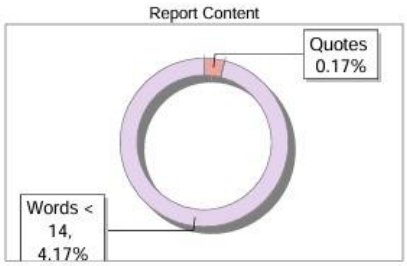

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Publication:

- ✓ **Ritu**, Verma, R., Kaushik, S., Kaur, P., Mathur, P., Velpandian, T., & Goyal, R. K. (2025). Hesperetin-supplemented soybean and ginger hydroalcoholic extracts alleviate diabetic cardiomyopathy in streptozotocin induced diabetic rats by modulating NF-κB/MMP-9/TIMPs pathway. *South African Journal of Botany*, *179*, 11-21.

- ✓ **Ritu** , Xiong, Y., Sharma, H. P., Goyal, R. K., Narwal, S., Berwal, A., Jain, S., ... & Singla, R. K. (2024). Bioflavonoid combination attenuates diabetes-induced nephropathy in rats via modulation of MMP-9/TIMP-1, TGF-β, and GLUT-4-Associated Pathways. *Heliyon*.

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- ✓ **RITU e**t al.,." Herbal Insights: Exploring the Therapeutic Potential of Indian Dietary Herbs in Diabetic Cardiomyopathy Management".Current Diabetes Reviews. 2024,July.

- ✓ **Dahiya, R**., Kaur, P., Goyal, K., Goyal, R. K., Singh, A., & Sharma, K. (2025). Uncovering the Impact of MMP-9 and TIMPs in Diabetic Nephropathy: A Review on Bioflavonoids in Disease Management. *Current Nutraceuticals*, *6*(1), E26659786333625.

- ✓ Kaur P, **Dahiya R**, Nandave M, Sharma K, Goyal RK. Unveiling the crucial role of intercellular adhesion molecule-1 in secondary diabetic complications. Cell Biochem Funct. 2024;42:e4037. doi:10.1002/cbf.4037.

- ✓ Kaur, P., **Ritu,** Sharma, K., & Goyal, R. K. (2025). Mitigating Diabetic Cardiomyopathy: The Therapeutic Potential of a Poly Herbal Combination in Modulating ICAM-1, VCAM-1, and NF-κB Expression in Rat Model. *Cardiovascular & Hematological Disorders-Drug Targets*.

- ✓ **Ritu**, P. D., Priya, M., Agarwal, G., & Sangeeta, S. N. (2023). Current developments in Nano-based technology for Ocular Disease: Recent evidence, Barriers and Translational opportunities. *Latin American Journal of Pharmacy*, *42*(7), 74-88.
- ✓ **Ritu**, Prabhnain Kaur, Kalicharan sharma, Ramesh K Goyal. Modulating Effect of Phenolic Compounds on The Insulin Secretion in RIN 5F Cells and Streptozotocin Induced Diabetes Rats. Afr. J. Bio. Sc. 6(5) (2024).

- ✓ Shikha Goswami, Kalicharan Sharma, **Ritu** , Ramesh K Goyal. Swertiamarin and its analogues ameliorates diabetes-induced dyslipidemia by attenuating mitochondrial dysfunction through ACC-2 and CPT-1 signaling pathways. Afr.J.Bio.Sc. 6(Si3) (2024)

Book chapter

- ✓ **Dahiya, R**., Buttar, H. S., & Gupta, S. K. (2022). Pathophysiology of Diabetes-Induced Complications: Promising Therapeutic Role of Dietary Flavonoids and Flavonoid Supplements in the Management of Diabetic Complications. Handbook of Nutraceuticals and Natural Products: Biological, Medicinal, and Nutritional Properties and Applications, 2, 397 421.

- ✓ Prabhnain Kaur, **Ritu Dahiya**, Ginpreet Kaur, Harpal S. Buttar, Douglas W. Wilson, Istvan G. Telessy ;Pathogenesis of Atherosclerosis and Coronary Heart Disease: Epidemiology, Diagnostic Biomarkers and Prevention by Nutraceuticals, Functional Foods, and Plant-Derived Therapies, Botanicals and Natural Bioactives: Prevention and Treatment of Diseases Bentham Briefs in Biomedicine and Pharmacotherapy (2024) 2: 146. https://doi.org/10.2174/9789815238273124020010
- ✓ Kaur, P., **Dahiya, R**., Buttar, H.S., Wilson, D.W., De Meester, F., Telessy, I.G. (2024). Antiatherogenic Effects of Vitamins, Mediterranean Diet and DASH Diet: An Overview for the Prevention of Cardiovascular Diseases. In: Shah, A.K., Tappia, P.S., Dhalla, N.S. (eds) Hydrophilic Vitamins in Health and Disease. Advances in Biochemistry in Health and Disease, vol 29. Springer, Cham. Chapter 3, Pages 45-66 https://doi.org/10.1007/978-3-031-55474-2_3

Conference/workshop/seminars:

Oral presentations

Dahiya, R., Goyal R.K. "In-Silico and In–Vitro Study Of Selected Bioflavonoids on NF-kB Mediated MMP 9 Pathway: Implication In Management Of Diabetic Complications" 2022 (4 Nov to 6 Nov) at Deshbandhu College, University of Delhi.

CONFERENCES ATTENDED

1. Presented **poster** at the International Conference of Cardiovascular Sciences (ICCS)-2020 on Artificial intelligence held on 21-23rd February 2020
2. International Symposium on "Safety Assessment under Materiovigilance and Pharmacovigilance Programs" held at Delhi Pharmaceutical Sciences and Research University, Delhi.
3. Annual conference- DPSCON 2023 on "Advances & Current Trends in Pharmacology" held at DPSRU, New Delhi
4. Presented **poster** at Indian eye research group (ARVO) -2023 on Bioflavonoids attenuate diabetic retinopathy by down-regulating the MMP-9 and NF-κB expression in diabetic rats held on 28-30 July 2023

Signature of Student **Signature of Supervisor**

Annexure

DELHI PHARMACOLOGICAL SOCIETY

2nd Annual Conference

DPSCON 2023

Certificate of Participation

This is to certify that Prof./Dr./Mr./Ms. Ritu has participated as Chairperson/Invited Speaker/Presenter in scientific session/Delegate in the conference held on 1st March, 2023 at DPSRU, Pushp Vihar, New Delhi.

Prof. RK Goyal
Chairman, DPS

Prof. T Velpandian
General Secretary, DPS

Kavita Gulati
Prof. K Gulati
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November 4th – 6th, 2022

Certificate of Participation

This Certificate is presented to **RITU DAHIYA**

for **oral presentation** of the paper entitled: "*In-Silico And In –Vitro Study Of Selected Bioflavonoids on NF-Kb Mediated MMP 9 Pathway: Implication In Management Of Diabetic Complications*"

in the conference **ICNPHH – 2022** held at Deshbandhu College, University of Delhi, New Delhi, India.

Dr. Sunil Kayesth
Coordinator, ICNPHH 2022

Prof. Kamal Kumar Gupta
Vice Principal, Deshbandhu college

Prof. Rajiv Aggarwal
Principal, Deshbandhu college

ARVO International Chapter Affiliate

ARVO-INDIA

Indian Eye Research Group

July 29-30, 2023

Certificate of Participation

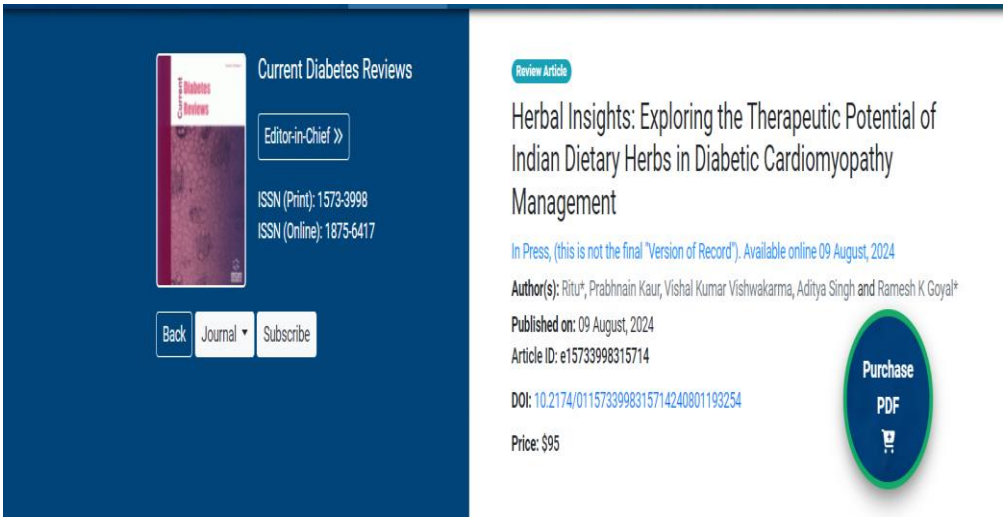
This is to certify that

Ritu Dahiya

participated and presented a paper/poster in the meeting held at Aravind Medical Research Foundation, Madurai.

Prof. K. Dharmalingam
President, ARVO-India

Dr. A. Vanniarajan
on behalf of Organisers



Current Diabetes Reviews

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Review Article

Herbal Insights: Exploring the Therapeutic Potential of Indian Dietary Herbs in Diabetic Cardiomyopathy Management

In Press, (this is not the final "Version of Record"). Available online 09 August, 2024

Author(s): Ritu*, Prabhnain Kaur, Vishal Kumar Vishwakarma, Aditya Singh and Ramesh K Goyal*

Published on: 09 August, 2024

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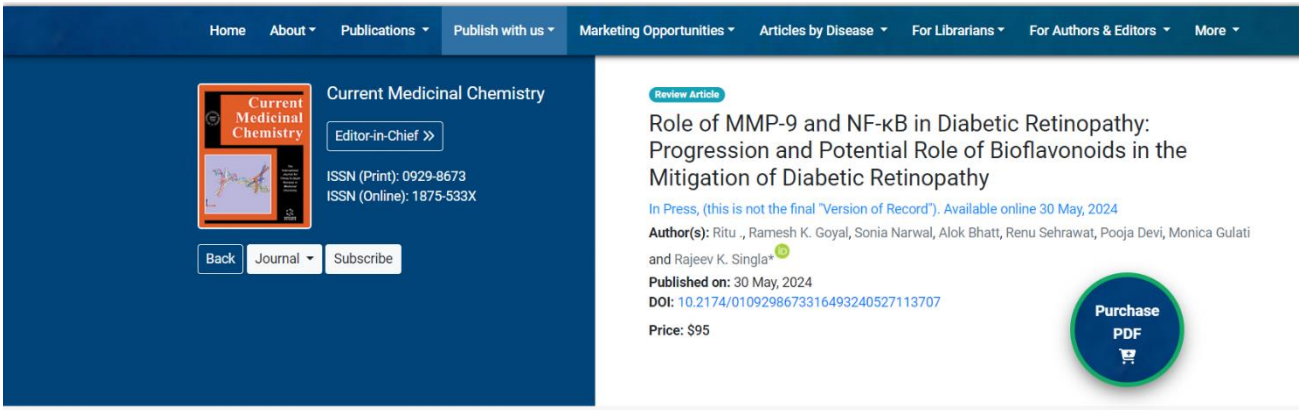
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Review Article
Role of MMP-9 and NF-κB in Diabetic Retinopathy: Progression and Potential Role of Bioflavonoids in the Mitigation of Diabetic Retinopathy
In Press, (this is not the final "Version of Record"). Available online 30 May, 2024
Author(s): Ritu ., Ramesh K. Goyal, Sonia Narwal, Alok Bhatt, Renu Sehrawat, Pooja Devi, Monica Gulati and Rajeev K. Singla*
Published on: 30 May, 2024
DOI: 10.2174/0109298673316493240527113707
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Review
Cell Biochem Funct. 2024 Jun;42(4):e4037. doi: 10.1002/cbf.4037.
Unveiling the crucial role of intercellular adhesion molecule-1 in secondary diabetic complications
Prabhnain Kaur [1], Ritu Dahiya [1], Mukesh Nandave [1], Kalicharan Sharma [2], Ramesh K Goyal [1]
Affiliations + expand
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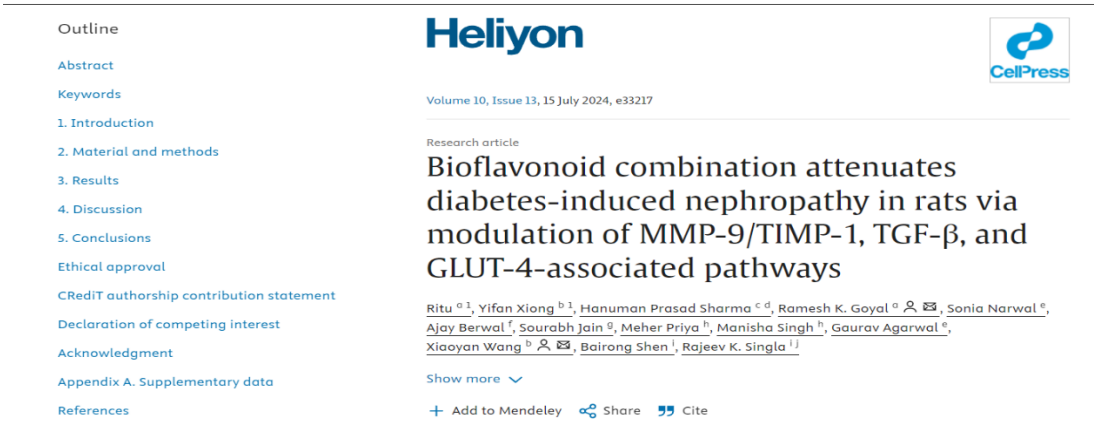
Outline
Abstract
Keywords
1. Introduction
2. Material and methods
3. Results
4. Discussion
5. Conclusions
Ethical approval
CRediT authorship contribution statement
Declaration of competing interest
Acknowledgment
Appendix A. Supplementary data
References
Heliyon
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Volume 10, Issue 13, 15 July 2024, e33217
Research article
Bioflavonoid combination attenuates diabetes-induced nephropathy in rats via modulation of MMP-9/TIMP-1, TGF-β, and GLUT-4-associated pathways
Ritu [a 1], Yifan Xiong [b 1], Hanuman Prasad Sharma [c d], Ramesh K. Goyal [a], Sonia Narwal [e], Ajay Berwal [f], Sourabh Jain [g], Meher Priya [h], Manisha Singh [h], Gaurav Agarwal [e], Xiaoyan Wang [b], Bairong Shen [i], Rajeev K. Singla [i j]
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African Journal of Biological Sciences

Modulating Effect of Phenolic Compounds on The Insulin Secretion in RIN 5F Cells and Streptozotocin Induced Diabetes Rats

Ritu[1#], Prabhnain Kaur[1#], Kalicharan Sharma[2], Ramesh K. Goyal[1*]

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South African Journal of Botany
Volume 179, April 2025, Pages 11-21

Hesperetin-supplemented soybean and ginger hydroalcoholic extracts alleviate diabetic cardiomyopathy in streptozotocin induced diabetic rats by modulating NF-κB/MMP-9/TIMPs pathway

Ritu [a b], Ravinder Verma [c], Sudhir Kaushik [d], Prabhnain Kaur [a], Pooja Mathur [b], T. Velpandian [e], Ramesh K Goyal [a]

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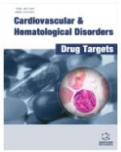
Highlights

- To explore the effect of Hesperetin, soy extract, and ginger extract on DC in rats induced by streptozotocin (STZ)
- Parameters like biochemical markers, ECG, echocardiography (ECHO), molecular pathways (NF-κB, MMP-9, TIMP-1), and histopathology were analyzed.
- Hesperetin, soy extract, and ginger extract combination significantly lowered fasting blood glucose, HOMA-IR, reduced fibrosis, improved myocardial structure and serum insulin levels.
- NF-κB, MMP-9 (promoting inflammation and tissue remodeling), and TGF-β were significantly downregulated, indicating protection against diabetic cardiac damage.



Mitigating Diabetic Cardiomyopathy: The Therapeutic Potential of a Poly Herbal Combination in Modulating ICAM-1, VCAM-1, and NF-κB Expression in Rat Model

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Authors: Prabhnain Kaur[1], Ritu[1,2], Kalicharan Sharma[3] and Ramesh Kumar Goyal[1]

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Source: Cardiovascular & Haematological Disorders - Drug Targets

Available online: 09 July 2025

DOI: https://doi.org/10.2174/011871529X374139250629193251

Received: 13 Dec 2024 **Accepted:** 19 Mar 2025 **Available online:** 09 Jul 2025

Background

Diabetic Cardiomyopathy (DCM) remains a significant health concern, necessitating innovative therapeutic approaches. This study explores the potential of a polyherbal combination (PHC) in mitigating DCM and delves into the underlying molecular

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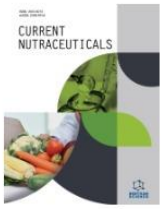

Uncovering the Impact of MMP-9 and TIMPs in Diabetic Nephropathy: A Review on Bioflavonoids in Disease Management

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Source: Current Nutraceuticals, Volume 6, Issue 1, Jan 2025, E26659786333625

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